

# PATENT SPECIFICATION

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NO DRAWINGS.

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## COMPLETE SPECIFICATION.

### $\alpha$ -Ethyl-phenylacetylurea.

We, LABORATOIRES SAPOS, S.A., a Swiss Body Corporate, of 5 rue Gustave-Moynier, Geneva, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement :—

This invention is concerned with improvements in or relating to new compounds of particular use in the treatment of epilepsy and like conditions.

Many compounds have been proposed for the treatment of epilepsy and like conditions, but many of the compounds used suffer from the disadvantage that they have a dormitive as well as an anti-epileptic effect. Thus, a patient being treated with such compounds becomes drowsy which is very inconvenient in everyday life. A further drug also widely used as an anti-epileptic is racemic  $\alpha$ -ethyl-phenylacetylurea also known as pheneturide, which also suffers from disadvantages.

We have now found however that the *d*- and *l*-isomers of  $\alpha$ -ethyl-phenylacetylurea, which are new compounds, possess unexpected therapeutic properties, which make it possible to administer them in the treatment of epilepsy and like conditions substantially without any sedative, soporific or excitant effects on the patient. Thus, we have unexpectedly found that whilst both

the *d*- and *l*-isomers have an anti-epileptic activity, the *d*-isomer has an excitant action whereas the *l*-isomer has a sedative action.

The excitant properties of the said *d*-isomer accordingly make it possible to formulate an anti-epileptic composition having substantially no sedative, soporific or excitant properties; thus if one mixes with the said *d*-isomer just sufficient of a sedative and/or soporific drug (e.g. a barbiturate) substantially to neutralise the excitant properties of the *d*-isomer one obtains a composition possessing on administration anti-epileptic properties but no, or substantially no, sedative or soporific properties. In particular one can just neutralise the excitant properties of the *d*-isomer by mixing with it sufficient of the anti-epileptic but sedative *l*-isomer so that an essentially anti-epileptic composition results with no or substantially no undesirable sedative or soporific effects, or excitant effects.

The invention thus includes especially the optically active *d*- $\alpha$ -ethyl-phenylacetylurea. It also includes optically active *l*- $\alpha$ -ethyl-phenylacetylurea.

These two compounds have the physical properties set out below which were determined for the purest material we have so far obtained. The corresponding properties of racemic  $\alpha$ -ethyl-phenylacetylurea are also given for purposes of comparison :

	M.P.	$[\alpha]_D^{20}$ (EtOH $c = 0.01\%$ )
<i>d</i> - $\alpha$ -ethyl-phenylacetylurea	168—169° C.	+54°
<i>l</i> - $\alpha$ -ethyl-phenylacetylurea	162—163° C.	— 51.6°
Racemic $\alpha$ -ethyl-phenylacetylurea	147—148° C.	0°

[Price 3s. 6d.]

According to a feature of the invention we provide compositions for the treatment of epilepsy and like conditions comprising  $d$ - $\alpha$ -ethyl-phenylacetylurea together with one or more drugs having a soporific and/or sedative action, the amount of such drugs present being such that the composition on administration causes substantially no excitative, sedative or soporific effects. Such drugs include barbiturates and in particular  $L$ - $\alpha$ -ethyl-phenylacetylurea which itself has a sedative action. Other sedative and/or soporific drugs which can be used include phenacemide and anti-convulsant drugs such as diphenyl hydantoin.

Particularly preferred compositions according to the invention are those containing both  $d$ - and  $L$ - $\alpha$ -ethyl-phenylacetylurea, in which the ratio of the former to the latter is from 1:3 to 1:1.25 by weight, preferably 30 to 40 parts by weight of the  $d$ -isomer to

60 to 70 parts by weight of the  $L$ -isomer.

The most effective composition is one containing 65 parts by weight of the  $L$ -isomer and 35 parts by weight of the  $d$ -isomer.

The present invention does not of course include the racemic mixture of the  $d$ - and  $L$ -isomers of the invention, which mixture has substantial excitative properties, or compositions containing the said racemic mixture.

Where a barbiturate or other sedative or soporific is used in conjunction with the  $d$ -isomer, the proportion of the barbiturate employed will vary from compound to compound. Barbiturates which can very satisfactorily be used include "Dial" (Registered Trade Mark), "Prominal" (Registered Trade Mark), secobarbital, butabarbital, veronal and phenobarbital. The action of the  $d$ -isomer in reducing the soporific effect of various barbiturates is shown in the following table:—

Action of  $d$ - $\alpha$ -ethyl-phenylacetylurea on barbiturate-induced sleep in the guinea pig.

Barbiturate	Dose mg/kg. per os	$d$ -isomer dose in mg/kg. per os	number of animals	mean sleep period in minutes	Percentage increase or diminution in sleep period compared with controls
"DIAL" (Registered Trade Mark)	30 30	50 —	5 5	146 202	- 28%
"PROMINAL" (Registered Trade Mark)	60 60	50 —	5 5	57 88	- 35%
SECOBARBITAL	15 15	50 —	5 5	108 168	- 35.7%
BUTABARBITAL	40 40	100 —	5 5	113 136	- 17%
VERONAL	50 50	50 —	5 5	54 90	- 40%
PHENOBARBITAL	30 30	50 —	5 5	42 51	- 18%

It will be understood that the  $L$ -isomer of  $\alpha$ -ethyl-phenylacetylurea is useful in itself when it is desired to treat epilepsy with a drug also having a sedative action. The  $d$ -isomer itself is also useful when treatment of epilepsy with a drug also having an excitative action is required.

The new optically active isomers according to the invention can be prepared in any convenient manner. Thus, for example, one can react the appropriately optically active acid chloride with urea to give the

desired  $\alpha$ -ethyl-phenylacetylurea. The reaction may be carried out in a number of ways such as those already proposed for the production of the racemic  $\alpha$ -ethyl-phenylacetylurea, all of which methods consist in reacting the components in a common solvent in the presence of an acid-binding agent. The purity of the product and the yields obtained using such methods are not, however, very high.

We have found however, that by carrying out the reaction in the absence of solvent

then products are obtained of greater purity and in higher yields than when carrying out the reaction in a solvent.

According to a further feature of the invention therefore we provide a process for the preparation of  $\alpha$ -ethyl-phenylacetylurea, in particular the *d*- and *l*-isomers thereof, which comprises reacting  $\alpha$ -ethyl-phenylacetyl chloride or a *d*- or *l*-isomer thereof with urea in the presence of an acid-binding agent in the absence of solvent.

The process according to the invention can conveniently be carried out by reacting the components at an elevated temperature, for example at 75–150° C., in the presence of a suitable acid-binding agent, such as, for example "Antipyrine" (Registered Trade Mark) or an alkali-metal bicarbonate such as sodium bicarbonate.

The acid chlorides used as starting material may be prepared from the corresponding acid, e.g. by treatment with thionyl or sulphuryl chloride. The optically active themselves from which the acid chlorides can be derived can be prepared by resolution of racemic  $\alpha$ -ethyl-phenylacetic acid in any suitable manner. We have found it convenient to effect the resolution by treatment of the acid with a suitable optically active base, followed by fractional crystallization, the optically active acids being liberated from the salts so formed. A suitable base for effecting the resolution is cinchonidine, the *d*- $\alpha$ -ethyl-phenylacetic acid salt of this base being less soluble than the *l*-isomer salt. It is preferred to carry out the resolution in ethyl alcohol of approximately 50% strength as it is possible thereby to obtain the two acids in a higher degree of purity. The *l*-isomer is preferably further purified after liberation from the cinchonidine salt by isolation as the codeine salt, from which the acid is again liberated.

The new compounds according to the invention can be presented in any desired manner for administration in conjunction with a pharmaceutical carrier. Thus, they may be presented in solid form, for example, as tablets or capsules or may be formulated in liquid form suitable for oral administration, for example, as syrups and elixirs, which may contain flavouring agents if desired.

The compounds according to the invention may also be made up in a form suitable for injection.

In order that the invention may be well understood the following examples are given by way of illustration only:—

#### EXAMPLE 1.

##### *d*- $\alpha$ -ethyl-phenylacetylurea.

2 molecular proportions of dry urea are mixed with 1 molecular proportion of "Antipyrine" (Registered Trade Mark) and

the mixture placed in a round-bottomed flask provided with a stirrer. 1 molecular proportion of *d*- $\alpha$ -ethyl-phenylacetyl chloride is then poured onto this mixture at room temperature, the stirrer being left turning for 15 minutes until a thick white paste forms. The contents of the flask are then slowly heated whilst stirring is maintained, the reaction mass melting at about 75° C., and changing into a colourless single phase. It is then heated for 1 hour at 100° C., when stirring is stopped as it becomes difficult due to thickening of the reaction mixture. Heating is continued on an oil bath to a temperature of 125–130° C. when the reaction mixture again melts so that stirring can be recommenced. After heating for 1 hour reaction is complete. An almost pure product crystallises out and can be recovered by filtration in a yield of 75% of the theoretical.

#### EXAMPLE 2.

##### *l*- $\alpha$ -ethyl-phenylacetylurea.

This may be prepared in a manner similar to that described in Example 1 but using *l*- $\alpha$ -ethyl-phenylacetyl chloride in place of *d*- $\alpha$ -ethyl-phenylacetyl chloride.

#### EXAMPLE 3.

The following example describes the preparation of *d*- and *l*- $\alpha$ -ethyl-phenylacetylurea from racemic  $\alpha$ -ethyl-phenylacetic acid.

##### (a) Preparation of *d*- $\alpha$ -ethyl-phenylacetic acid.

200 g. of racemic  $\alpha$ -ethyl-phenylacetic acid and 300 g. of cinchonidine (free base) is dissolved in 2 litres of 50% ethyl alcohol. There crystallises 360 g. of a salt the free acid from which shows an optical rotation of  $[\alpha]_D^{20} = +58.2^\circ$  ( $c = 0.026$  in benzene) and contains 80% of the *d*-isomer. The melting point of the crude salt is 100° C.

The 360 g. of the crude salt recrystallized from 1500 mls. of 50% alcohol gave 800 g. of a salt, the free acid of which gave an optical rotation of  $[\alpha]_D^{18} = +68.5^\circ$  ( $c = 0.0533$  in benzene). The same operation is repeated three times and results in an optically pure salt having m.p. = 127° C. The free acid has  $[\alpha]_D^{16} = +96.6^\circ$  ( $c = 0.015$  in benzene). Yield 60%.

##### (b) Preparation of *l*- $\alpha$ -ethyl-phenylacetic acid.

To the mother liquors from the first two crystallizations above are added 55 g. of cinchonidine (free base) when the cinchonidine salt of the *l*-isomer crystallizes out. The free acid has  $[\alpha]_D^{16} = -65^\circ$  ( $c = 0.014$  in benzene) and contains 84% of the *l*-isomer. The appearance of this salt of cinchonidine is different from that of the *d*-isomer, as it is

By 25

- flocculant, light and crystallizes very slowly. On repeated recrystallization from 50% ethyl alcohol, a salt giving an optically pure acid  $[\alpha]_D^{19} = -96.0^\circ$  ( $c = 0.0136$  in benzene) is obtained.
- Having removed the dextrorotatory salt of cinchonidine from the mother liquors, the laevorotatory acid can advantageously be liberated therefrom by treatment with concentrated hydrochloric acid, extraction with benzene, removal of the solvent and purification of the laevorotatory acid as follows:—
- 6.3 g. of the crude laevorotatory acid are dissolved in 120 mls of boiling ethanol and 11.6 g. of codeine (free base) are added. Crystallization takes place slowly, yielding the codeine salt, the free acid of which has  $[\alpha]_D^{18} = -75^\circ$  ( $c = 0.948$  in benzene). After two recrystallizations from water, the codeine salt is obtained optically pure (m.p.  $159^\circ$  C.). The free acid has  $[\alpha]_D^{19} = -96.0^\circ$  ( $c = 0.0245$  in benzene). Yield 20%.
- (c) *Preparation of d- $\alpha$ -ethyl-phenylacetyl chloride.*
- By the action of an excess of thionyl chloride on d- $\alpha$ -ethyl-phenylacetic acid there is obtained the acid chloride having a boiling point of  $108-107^\circ$  C. (20 Tore),  $[\alpha]_D^{18} = +108^\circ$  ( $c = 0.02$  in benzene).
- (d) *Preparation of l- $\alpha$ -ethyl-phenylacetyl chloride.*
- By the same reaction as (c) above there is obtained the acid chloride of l- $\alpha$ -ethyl-phenylacetic acid of boiling point  $109-110^\circ$  C. (20 Tore),  $[\alpha]_D^{19} = -107^\circ$  ( $c = 0.02$  in benzene).
- (e) *Preparation of d- $\alpha$ -ethyl-phenylacetylurea.*
- 12.8 g. of d- $\alpha$ -ethyl-phenylacetyl chloride are mixed in the cold with shaking in a 150 mls. flask with 9.6 g. of pure dry urea and 16 g. of antipyrine. The mixture is shaken for 15 minutes in the cold then heated gently on a water bath to  $100^\circ$  C. and maintained at this temperature for 30 minutes. The colourless mass melts a little at a time. When the reaction is finished the temperature is maintained at  $125-130^\circ$  C. for a further 20 minutes. With constant stirring 50 mls. of 96% ethyl alcohol and 5 mls. of 10%  $\text{Na}_2\text{CO}_3$  are added. The clear solution is then added to 65 mls. of water, the d- $\alpha$ -ethyl-phenylacetylurea crystallizing as white needles. Yield 13.02 g. (75%). Recrystallization from 80 c.c.s. of 96% alcohol gives the pure d-isomer of m.p.  $168-169^\circ$  C.  $\text{C}_{11}\text{H}_{14}\text{O}_2\text{N}_2$  Calculated  
C: 64.00%, H: 6.70%, N: 13.59%
- Found  
C: 64.03%, H: 6.75%, N: 13.00%
- $[\alpha]_D^{20} = +54.0^\circ$  ( $c = 0.01$  in ethyl alcohol) 60  
 $[\alpha]_D^{22} = +53.8^\circ$  ( $c = 0.01$  in acetone)  
 $[\alpha]_D^{22} = +48.2^\circ$  ( $c = 0.01$  in dioxan)
- (f) *Preparation of l- $\alpha$ -ethyl-phenylacetylurea.*
- 3.6 g. of l- $\alpha$ -ethyl-phenylacetyl chloride, 2.5 g. of urea and 4.25 g. of "Antipyrine" (Registered Trade Mark) are reacted as for (e) above and after crystallization from 50% alcohol, 3.223 g. of l- $\alpha$ -ethyl-phenylacetylurea (70% yield) are obtained, m.p.  $162-163^\circ$ .  $\text{C}_{11}\text{H}_{14}\text{O}_2\text{N}_2$  Calculated  
C: 64.00%, H: 6.70%, N: 13.59%
- Found  
C: 64.10%, H: 6.68%, N: 13.68%
- $[\alpha]_D^{20} = -51.6^\circ$  ( $c = 0.01$  in ethyl alcohol) 75
- WHAT WE CLAIM IS:—
1. The optically active isomers of  $\alpha$ -ethyl-phenylacetylurea.
  2. A composition for the treatment of epilepsy and like conditions having substantially no sedative, soporific or excitatory properties comprising d- $\alpha$ -ethyl-phenylacetylurea together with one or more drugs having a soporific and/or sedative action.
  3. A composition as claimed in Claim 2 in which said drugs include barbiturates and/or other anticonvulsant drugs.
  4. A composition as claimed in Claim 2 in which said drugs include l- $\alpha$ -ethyl-phenylacetylurea.
  5. A composition as claimed in Claim 4 in which the ratio of d- $\alpha$ -ethyl-phenylacetylurea to l- $\alpha$ -ethyl-phenylacetylurea is from 1:3 to 1:1.25 parts by weight.
  6. A composition as claimed in Claim 5 in which the ratio of d- $\alpha$ -ethyl-phenylacetylurea to l- $\alpha$ -ethyl-phenylacetylurea is 30 to 40 parts of the former to 60 to 70 parts of the latter.
  7. A composition as claimed in Claim 6 100 in which the ratio of d- $\alpha$ -ethyl-phenylacetylurea to l- $\alpha$ -ethyl-phenylacetylurea is 35 parts by weight of the former to 65 parts by weight of the latter.
  8. Compositions as claimed in Claim 2 105 for the treatment of epilepsy and like conditions substantially as herein described.
  9. A process for the preparation of  $\alpha$ -ethyl-phenylacetylurea which comprises reacting  $\alpha$ -ethyl-phenylacetyl chloride with urea in the presence of an acid binding agent and in the absence of solvent.
  10. A process as claimed in Claim 9 for

the preparation of the *d*- or *L*-isomer of  $\alpha$ -ethyl-phenylacetylurea in which the *d*- or *L*-isomer of  $\alpha$ -ethyl-phenylacetyl chloride is used as starting material.

11. A process as claimed in Claim 9 or Claim 10 in which the reaction is carried out at elevated temperature.

12. A process as claimed in Claim 11 in which the reaction is carried out at a temperature of from 75—160° C.

13. A process as claimed in any of Claims 9—12 in which the acid-binding agent is "Antipyrine" (Registered Trade Mark) or an alkali-metal bicarbonate.

14. A process as claimed in any of Claims 10—13 in which the *d*- or *L*-isomers of  $\alpha$ -ethyl-phenylacetyl chloride are obtained by reaction of the corresponding optically active acids with thionyl or sulphuryl chloride.

15. A process as claimed in Claim 14 in which the optically active acids are obtained from racemic  $\alpha$ -ethyl-phenylacetic acid by resolution thereof with an optically active base followed by fractional crystallization of the resulting salts and recovery of the optically active acids therefrom.

16. A process as claimed in Claim 15 in which the base is cinchonidine.

17. A process as claimed in Claim 16 in which the fractional crystallization is effected in approximately 50% aqueous ethyl alcohol.

18. A process as claimed in Claim 16 for the preparation of *L*- $\alpha$ -ethyl-phenylacetic acid in which the acid is purified after liberation from the cinchonidine salt by isolation as the codeine salt thereof from which the acid is again liberated.

19. A process for the preparation of the *d*- and *L*-isomers of  $\alpha$ -ethyl-phenylacetylurea substantially as herein described with reference to any of the examples.

20.  $\alpha$ -Ethyl-phenylacetylurea and the *d*- and *L*-isomers thereof when prepared by a process as claimed in any of Claims 9—19 or an obvious chemical equivalent thereof.

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## PROVISIONAL SPECIFICATION.

### $\alpha$ -Ethyl-phenylacetylurea.

We, LABORATOIRES SAPOS, S.A., a Swiss Body Corporate, of 5 rue Gustave-Meynier, Geneva, Switzerland, do hereby declare this invention to be described in the following statement:—

This invention is concerned with improvements in or relating to new compounds of particular use in the treatment of epilepsy and like conditions.

Many compounds have been proposed for the treatment of epilepsy and like conditions, but most of the compounds used suffer from the disadvantage that they have a dormitive as well as an anti-epileptic effect.

Thus, a patient being treated with such compounds becomes drowsy which is very inconvenient in everyday life. One of the compounds most widely used is  $\alpha$ -ethyl-phenylacetylurea also known as pheneturide. In common, however, with most other anti-epileptic drugs this compound also suffers from the disadvantage of producing drowsiness.

We have now found however that the *D*- and *L*-isomers of  $\alpha$ -ethyl-phenylacetylurea, which are new compounds, possess unexpected therapeutic properties, which make it possible to administer them in the treatment of epilepsy and like conditions without the patient becoming drowsy. Thus, we have unexpectedly found that whilst

both the *D*- and *L*-isomers have an anti-epileptic activity, the *D*-isomer has an excitive action and not, as is common with most anti-epileptic drugs, a sedative action. The *L*-isomer has a sedative action.

The excitive properties of the said *D*-isomer accordingly make it possible to formulate an anti-epileptic composition having substantially no sedative or excitive properties; thus if one mixes with the said *D*-isomer just sufficient of a soporific drug (e.g. a barbiturate) to neutralise the excitive properties of the *D*-isomer one obtains a composition possessing on administration anti-epileptic properties but no, or substantially no, sedative or soporific properties. In particular one can just neutralise the excitive properties of the *D*-isomer by mixing with it sufficient of the anti-epileptic but sedative *L*-isomer so that an essentially anti-epileptic composition results with no or substantially no undesirable sedative or soporific effects, or excitive effects.

The invention thus includes especially the optically active *D*- $\alpha$ -ethyl-phenylacetylurea. It also includes optically active *L*- $\alpha$ -ethyl-phenylacetylurea.

These two compounds have the physical properties set out below which were determined for the purest material we have so far obtained. The corresponding properties of

racemic  $\alpha$ -ethyl-phenylacetylurea are also given for purposes of comparison :—

	M.P.	$[\alpha]_D^{20}$ (EtOH)
D- $\alpha$ -ethyl-phenyl-acetylurea	168—169	+54°
L- $\alpha$ -ethyl-phenyl-acetylurea	162—163	-51.6°
Racemic $\alpha$ -ethyl-phenylacetylurea	147—148	0°

- 10 According to a feature of the invention we provide compositions for the treatment of epilepsy and like conditions comprising D- $\alpha$ -ethyl-phenylacetylurea if desired, together with a proportion of L- $\alpha$ -ethyl-phenylacetylurea and/or one or more other drugs having a sedative action, in particular barbiturates, in which the proportion of D- $\alpha$ -ethyl-phenylacetylurea to the drugs having a sedative action is such that on administration substantially no sedative or excitant effects are caused.

- 25 The new optically active isomers according to the invention can be prepared in any convenient manner. Thus, for example, one can react the appropriate optically active acid chloride with urea to give the desired  $\alpha$ -ethyl-phenylacetylurea. This reaction may be carried out in a number of ways such as those already proposed for the production of the racemic  $\alpha$ -ethyl-phenylacetylurea, all of which methods consist in reacting the components in a common solvent in the presence of an acid-binding agent. The purity of the product and the yields obtained using such methods are not, however, very high.

- 35 We have found however, that by carrying out the reaction in the absence of solvent then products are obtained of greater purity and in higher yields than when carrying out the reaction in a solvent.

- 40 According to a further feature of the invention therefore we provide a process for the preparation of  $\alpha$ -ethyl-phenylacetylurea, in particular the D- and L-isomers thereof, which comprises reacting  $\alpha$ -ethyl-phenylacetyl chloride or a D- or L-isomer thereof with urea in the presence of an acid-binding agent in the absence of solvent.

- 50 The process according to the invention can conveniently be carried out by reacting the components at an elevated temperature for example at 75—150° C. in the presence of a suitable acid-binding agent, such as, for

example "Antipyrine" (Registered Trade Mark), or an alkali-metal bicarbonate such as sodium bicarbonate.

The new compounds according to the invention can be presented in any desired manner for administration. Thus, they may be presented in solid form, for example, as tablets or capsules or may be formulated in liquid form suitable for oral administration, for example, as syrups and elixirs, which may contain flavouring agents if desired.

The compounds according to the invention may also be made up in a form suitable for injection.

In order that the invention may be well understood the following examples are given by way of illustration only :—

#### EXAMPLE 1.

##### D- $\alpha$ -ethyl-phenylacetylurea.

2 molecular proportions of dry urea are mixed with 1 molecular proportion of antipyrine and the mixture placed in a round-bottomed flask provided with a stirrer. 1 molecular proportion of D- $\alpha$ -ethyl-phenylacetyl chloride is then poured onto this mixture at room temperature, the stirrer being left turning for 15 minutes until a thick white paste forms. The contents of the flask are then slowly heated whilst stirring is maintained, the reaction mass melting at about 75° C. and changing into a colourless single phase. It is then heated for 1 hour at 100° C. when stirring is stopped as it becomes difficult due to thickening of the reaction mixture. Heating is continued on an oil bath to a temperature of 125—130° C. when the reaction mixture again melts so that stirring be recommenced. After heating for 1 hour reaction is complete. An almost pure product can be recovered in a yield of 75% of the theoretical.

#### EXAMPLE 2.

##### L- $\alpha$ -ethyl-phenylacetylurea.

This may be prepared in a manner similar to that described in Example 1 but using L- $\alpha$ -ethyl-phenylacetyl chloride in place of D- $\alpha$ -ethyl-phenylacetyl chloride.

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